cisplatinum doses as high as 225 mg/m^2. Doses higher than 100 mg/m^2 could be tested also in thymoma patients.

The results of our study highlight a few interesting points: (1) Patients may survive for prolonged periods despite disease relapse. (2) Freedom from relapse does not ensure longevity owing to late deaths from nonthymomatous causes. (3) Myasthenia in patients with stage IVa disease tends to persist. (4) There is a moderate rate of contralateral pleural relapse. (5) More than 10% of the patients are expected to have a second primary neoplasm. Pleuropneumonectomy, or extrapleural pneumonectomy in myasthenic patients and after neoadjuvant chemotherapy, may be associated with considerable mortality. Considering the entire spectrum of these facts along with life quality, we believe that the approach proposed by us, that is, lung-preserving resection plus HPCP, may emerge as the preferred treatment for thymoma patients with pleural spread.

Our study has some of the usual weaknesses of a single-center nonrandomized study: selection bias and confounding variables. The fact that the response rate to preoperative chemotherapy in thymoma patients was 88% points to a selection bias from referral centers. The contribution of various preoperative and postoperative modalities to survival could not be analyzed owing to a great variation in means and timing. A large prospective multicenter trial may overcome these shortcomings.

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Discussion

Dr Joshua R. Sonett *(New York, NY).* Dr Yellin, thank you for the delivery of your manuscript and your slides over a month before the presentation.

I have nothing to disclose except to personally thank you for helping bring this modality to Columbia over 7 years ago. I am glad to say that the patient you introduced this therapy to at Columbia is doing quite well.

Your group has to be complimented as one that thought outside the box about locoregional treatment before it was fashionable and is assessing it quite soberly and objectively even as you advocate it as a possible standard.

I have some general points of discussion and 3 questions. Your best results, as one might expect, were in R0 resections, as with virtually all thymic resection series. Many would thus argue that these patients do not need this therapy. Can you tackle this question and also help sort out how to definitively prove this is a significant therapeutic advance, especially given the overall slow progression of many of these patients and the ability to give subsequent systemic chemotherapy?

Induction chemotherapy for locally advanced thymoma appears to be effective in reducing tumor burden and increasing R0 resections. Would you at present advocate or consider systemic chemotherapy before your operative treatment with known stage IV disease to increase your R0 resection preoperatively?

Finally, at Columbia we have pretty much copied your model for advanced thymoma. However, in pleural mesothelioma we have developed a model of repeated intrapleural dosing. If chemotherapy given once intraoperatively is of probable but not proven value, why stop at a single dose? All conventional cancer chemotherapy is given repeatedly. Repetitive chemotherapy kills a greater

fraction of cells as well as cells that have emerged from a chemorefractory state. We have thus far shown in patients with pleural mesothelioma that such chemotherapy can be given over a 2-month period via indwelling intrapleural catheters, repeated quite safely and easily. So should we consider this model for stage IV thymomas, followed by a final resection and heated chemotherapy?

I thank you and again congratulate you on your pioneering work.

Dr Yellin. Thank you, Dr Sonett, for your kind remarks and thoughtful input.

I personally doubt that R0 resection is indeed achievable, although formally that is the case. The philosophy behind the perfusion is to treat invisible small implants. R0 resection yielded the best results as far as local control was concerned, but it had no impact on overall survival. Unfortunately, the proof that perfusion has an advantage over any other modality requires a phase 3 study, which probably will never take place.

Preoperative chemotherapy in our patients was given sporadically in an unplanned manner. It was not in a neoadjuvant setting. From our data, it seemed effective but had no impact on the results. Nevertheless, faced with an invasive mediastinal thymoma or bulky implants, I would recommend neoadjuvant therapy.

The third question is certainly very interesting. Before addressing it, I have to mention a few facts. First, pharmacokinetic studies have shown that in the perfusion setting, cisplatinum serum concentration is almost 0 after 24 hours, which allows for a second dose. Second, cisplatinum absorption is higher in patients undergoing limited resection compared with those who undergo extrapleural pneumonectomy. Third, perfusion is followed very quickly by severe adhesions. Therefore, I believe that we could indeed repeat the dose, but only in a time frame of about a week, not very much longer. We certainly should consider it. Thank you for the idea.

Dr David J. Sugarbaker *(Boston, Mass).* You chose platinum and doxorubicin as your 2 drugs. In terms of dosing, inasmuch as there are no data on the appropriate dose of chemotherapeutic agents placed intrathoracically, do you think that you might be better served by performing a phase 1 trial to establish the maximum tolerated dose? We have done that with mesothelioma, as presented earlier today. We achieved a dose that was several times higher than the dose that is given intravenously, 225 versus 100 mg/m^2. If you remember Hill's postulates on the effectiveness of chemotherapy, effective chemotherapy improves survival as one is able to increase the concentration and/or dose of the drug.

I have 2 questions. First, you selected doxorubicin and platinum. In the United States, that is not a commonly administered chemotherapeutic regimen for stage IV thymoma. Second, do you think that additional studies of the phase 1 type which would allow for dose escalation and triplets would allow you to maximize the effect of chemotherapy?

Dr Yellin. We chose cisplatinum and doxorubicin because those are 2 of the most common drugs given for thymoma at large and those are the drugs that worldwide have the largest experience. We know most about the pharmacokinetics, the side effects, and so on. We were concerned with the higher doses you have reached because, with an intact pleura, we should expect higher serum levels, and therefore toxicity could be a bit higher than is seen in other studies.

Dr Sugarbaker. Are you trying to get all macroscopic disease resected, in which case I would assume that the pleura was also resected? Is that not the case?

Dr Yellin. Not necessarily. In most cases we did not perform a total pleurectomy, only a partial pleurectomy. Certainly, the visceral pleura was intact and part of the mediastinal pleura was intact and the diaphragmatic pleura stayed intact. We had enough of an absorption area to increase serum levels.

Dr Sugarbaker. Do you think that all that retained pleura, which is invariably seeded with tumor cells, may be responsible somewhat for the survival that you noted? Do you think you might be better off to do a complete, radical pleurectomy in these cases if you are not going to do an extrapleural pneumonectomy?

Dr Yellin. Perhaps, but the survival results are at least comparable with those with extrapleural pneumonectomy, and therefore I am not sure it is indeed required.

Dr Mark J. Krasna *(Neptune, NJ).* I enjoyed the presentation and again congratulate you and your group for pushing this forward for many, many years.

As we heard this morning in the mesothelioma talk by Dr Sugarbaker, it sounds like your group is now using it, and now you are talking about putting it into a phase 2 study. The message that I would like to understand is, first, are you ready to say to us that in prime time we should do this? Are you advocating that off protocol we should be using intrapleural chemotherapy for the stage IV diseases, whether you do it as an extrapleural pneumonectomy or an en bloc macroscopic resection? My second question to both you and Dr Sugarbaker is, if not, can we get a cooperative group study? I know many years ago we tried to do a cooperative group study for mesothelioma to test your phase 2 hypothesis, David. Is it time to do either a national or international phase 2 or phase 3, either in the thymic group or the mesothelioma?

Dr Yellin. I certainly advocate it, but, unfortunately, the International Thymic Malignancy Interest Group has decided that another venue is maybe preferred owing to technical difficulties and institutional review board problems and so on. I believe this is the best thing to do, but certainly there are many ways to skin a cat.

Dr Sugarbaker. I would respond to your questions, Mark, with the following. This study in particular has relatively small numbers, and I do not think we can make conclusions as to standard of care from such a study. I think excellent groundwork has been laid in single institutional trials for a multi-institutional feasibility trial to see whether this is exportable. However, with all of the discussion going on about the performance of macroscopic complete resection by extrapleural pneumonectomy or pleurectomy by those who think that those 2 operations are done for the same indication, which they are not, it certainly indicates that, just like with lung transplantation that we just heard, esophageal cancer, and lobectomies earlier in this meeting, not everybody who does extrapleural pneumonectomy, particularly at low frequencies, is going to have the same perioperative mortality. The recent MARS (Mesothelioma And Radical Surgery) trial had an almost 20% operative mortality, an extremely small number of patients, and it really defies any conclusions at all about the appropriate procedure. As I mentioned this morning, depending on disease distribution, either

pleurectomy/decortication or extrapleural pneumonectomy, as long as you are getting 3% or 4% operative mortality for the pneumonectomies, should be applied to get a macroscopic complete resection. What we need to do is to move on, as you are suggesting and as the author here is suggesting, to determine what the better extender of surgical margin is in these 2 tumors that recur locally. What is the best regimen? I think that is where surgeons and oncologists should be going. We should drop this idea as to which operation is better, because it is really 2 different operations for 2 different indications and distributions of disease.